



Episode 255: Psychedelics and Headache Disorders

Lindsay Weitzel, PhD:

Hello everyone, and welcome to HeadWise, the videocast and podcast of the National Headache Foundation. I'm Dr. Lindsay Weitzel, and I have a history of chronic and daily migraine that began at the age of four. Thank you everyone for joining us today. I have a very special and awesome guest that has not been on HeadWise before. I am here today with Dr. Emmanuelle Schindler. Hello, Dr. Schindler. How are you?

Emmanuelle Schindler, MD, PhD:

Hi, Lindsay. I'm doing well. How are you?

Lindsay Weitzel, PhD:

I am good. Dr. Schindler is medical director of the Headache Center of Excellence at the VA Connecticut Healthcare System. She is also associate professor of neurology at Yale School of Medicine. She is responsible for the first controlled trials of psilocybin in cluster, migraine, and post-traumatic headache. And we are here to ask her some questions about that today. Now, we have had some people on talking about this topic, but we are going to get an update. We're going to get an angle that we've never had before. Dr. Schindler, let's first address the elephant in the room. There's a lot of stigma around the type of research you do, correct?

Emmanuelle Schindler, MD, PhD:

Yes. At my institutions I'm, years ago, known as the mushroom lady. Now I think people, I wouldn't say they didn't take it seriously before, they were just sort of waiting for more information. So, yes.

Lindsay Weitzel, PhD:

It's interesting because I am from Colorado, so I had to look up how many states psilocybin is legal in because being from Colorado, it is kind of part of the conversation. This is one of the states that is more accepting of this conversation, but I believe there's only three states that it's considered legal with some limitations. Is that true?

Emmanuelle Schindler, MD, PhD:

So, psilocybin and other psychedelics are all still Schedule 1, so on a federal level they're not legal. There are some states and cities that have decriminalized it so it's the lowest level of interest for police and other folks to go after people who might have it. And so, I actually would have to review that myself in terms of which locations can people obtain it. From my end as a researcher, no matter what, I have to get FDA approval to do the research. But yes, it is increasing, the states and the cities that

where it's been decriminalized. And we can use our lessons that we learned from cannabis in terms of how something that becomes more widely used and clearly has some medicinal benefits, might be managed. Cannabis remains Schedule 1 as well right now too.

Lindsay Weitzel, PhD:

Now that we've addressed that, for people that are wondering why on earth we can even talk about this or research it, we have addressed the elephant in the room. When I originally contacted you, I mentioned that I was hoping to discuss your data and also get the word out that psilocybin or psychedelics are being studied in the setting of migraine, not just cluster headache. Because we have discussed this topic in the setting of cluster headache before on HeadWise. So you corrected me because I did not use the term psychedelics. You said that you were hoping to discuss the broader topic of psychedelics and headache, not just psilocybin. Can you please clarify or just discuss for our audience these terms how they're used and how it's relevant to the topic?

Emmanuelle Schindler, MD, PhD:

Sure. So, the term psilocybin, that's the compound that is found in magic mushrooms or that can be synthesized outside of the mushroom as well. But that's just one of many psychedelics that are out there. And then the word psychedelic itself, depending on who you talk to, you may get a different definition of what that is. But I stick to the pharmacological definition, which is a compound that has serotonin 2A activation, and that acutely causes altered sensation, perception, and consciousness. These serotonin 2A receptor agonists are broken down into two different chemical classes. And these are the compounds like psilocybin, but also DMT (dimethyltryptamine), lysergic acid diethylamide (LSD), LSA, which can be found in certain seeds of flowering plants. So, there are a lot of naturally occurring and also synthetic psychedelics out there. And while psilocybin is the most studied and perhaps one of the easiest ones to obtain outside of a lab, there's a lot of data about the other psychedelics too.

Lindsay Weitzel, PhD:

I'm going to break from what I was thinking of where I was going to go next, just because I think a lot of people who might not have heard how this can be used in the setting of headache or migraine or cluster are wondering now, when these psychedelics are studied in headache or utilized, do people have to have these effects that you're discussing? Do you have to have these effects in order to feel better from your cluster or headache, your migraine, etc.?

Emmanuelle Schindler, MD, PhD:

So that's a big topic in psychedelic medicine in general, whether you're studying headache disorders, pain disorders, mental health disorders, because for headache disorders, it does not seem that you need to have the psychedelic experience to have the clinical benefit. For mental health disorders, it might be necessary. Although not all studies have found that patients need to have that experience either to have the clinical benefit. But then of course there are always patients who might need a higher dose of something and with a higher dose would naturally come psychedelic effects. But for the majority of cases, people don't need to have that psychedelic experience to have the clinical outcome. And if they need a higher dose just to treat their condition happens to come with psychedelic effects, that also doesn't necessarily mean that the experience they have is what's driving the outcome.

Lindsay Weitzel, PhD:

Let's start. Let's go into the data if you can. I wanted to start by summarizing some of the effects in cluster headache, since that's something we've discussed before. And then we can move on to some of your other data. Can you just quickly talk about how psychedelics can be helpful to patients who have cluster headache?

Emmanuelle Schindler, MD, PhD:

And since you mentioned that you've had had this topic before, I'll probably just be sort of repeating what we've learned before that the research that is being done with psilocybin and a cluster headache is taken from the patient experience, that they've been using psilocybin mushrooms for 25 years now and have found that doing a pulse treatment. So, the general one is the three doses of a low dose of psilocybin, five days apart each, that can break someone out of a cluster cycle or bring someone who has chronic cluster headache, the people who have headaches year-round, bring them to a temporary remission, or at least reduce how many attacks they're having.

So, this is what's known as a transitional effect in headache medicine. We already have other drugs that also do this. Think of the steroid pulse. When someone's got status migrainosus or someone is entering a cluster cycle, they take steroid pulse to quiet things down. Patients will also come into the hospital and get DHE (dihydroergotamine), which by the way is chemically very similar to LSD, just not psychedelic. They'll get a DHE pulse to break out of a cycle or reduce cluster headache burden. So, psilocybin has been studied as a as a transitional treatment for cluster headache.

Lindsay Weitzel, PhD:

And I believe many people in our audience are aware that cluster headache is one of the most painful conditions known to man, so this is hugely important data because of the suffering that it can help alleviate. And at clusterbusters.org, we have had Clusterbusters people on before, Bob Wold. We often talk about some of the advocacy that goes on with that organization. And so, we love to talk about cluster headaches since it gets less attention than migraine. So, if we can go ahead and move on because we haven't discussed on this podcast what happens or some of your data behind psychedelics and migraine.

Emmanuelle Schindler, MD, PhD:

Since there's not the same type of decades of patient experience coalescing into a nice regimen like the Clusterbusters group has done for migraine, when I started to study it. I started with a simpler concept. Just try that same dose that's used in cluster, but just one dose to see what happens. And in the first study that I published, it looked like one dose reduced headache frequency in migraine patients by half over the two-week period that I looked at. It was a very short-term study, so just for two weeks. But there's not many other or no drugs out there for migraine you can just take one dose of and have half as many migraines for two weeks. And when I called patients who took part in the study back at one month and two months, that some people said that those effects lasted even longer, that it was even out to a month or more, that they had fewer migraines. But that was a very small study. And the control agent was a fiber pill was what people were using back then for psychedelic studies as a placebo.

So, for a second study that was recently published, I did a couple of things. I used a better placebo. I used diphenhydramine, which some of us take at night to help us sleep. If you try to stay awake through diphenhydramine, you might feel a little bit buzzed, a little weird, and then fall asleep. And that's sort of what patients on this low dose of psilocybin would feel. They feel a little off, and then they get sleepy. So, I thought the hydrogen mine would be a pretty good drug to use as a placebo to try to have patients not really know what they're getting. And I wouldn't expect a single diphenhydramine to reduce your migraines by half for weeks or months.

And then a second part of that new study that I published was to consider, well, cluster headache patients pulse their psilocybin, what if pulsed it for migraine. So, I compared one versus two doses. It would be way too many groups to have one, 2 or 3, so I started out with just 1 or 2. So in this study it didn't seem like there was any difference between 1 or 2 doses of the psilocybin, so there was still the same reduction. And this study looked at a bit longer. I looked out over two months and there was, again, about a 50% reduction, whether patients got 1 or 2 doses of the psilocybin.

But I also had a group that just got diphenhydramine. And they also over those two months, got down to about half as many migraines as they had at the beginning. In the first month you see, it looks like the folks who got psilocybin maybe did a little bit better. And this study only had 5 or 6 patients in each group. So that's a very small number. By a hundred times more, it would probably be significant. But in this study, it didn't show that. But this is not a bad thing. It doesn't say that that psilocybin doesn't have promise as a transitional treatment in migraine. It actually looks more like regular migraine studies where there is a placebo effect.

In the first migraine study that I did where I used the fiber pill, there was no effect with the fiber pill. And so, people pretty much guessed what they got, whether they got the fiber pill or the or the psilocybin. So, in using diphenhydramine, I could show that, okay, I'm actually able to get a placebo effect that that looks more like what we see in studies with conventional medications. So again, we need larger studies to really see whether there is a difference. And part of what this study, this more recent study, showed was that maybe diphenhydramine can serve as that active control agent.

Lindsay Weitzel, PhD:

I do think that is one of the things I wanted to comment on is these studies. Right now, the phases we're in, they are so small and it is so early. And so it's something that I think we all want to pay attention to as we hopefully get larger and more studies. Were there any other types of headache that you've looked at that you wanted to comment on?

Emmanuelle Schindler, MD, PhD:

Yeah. So, I did look at patients who have post-traumatic headache. I do practice at a VA, and so a lot of patients have head injury or blast wave injury and have headaches afterwards. And they're kind of a different animal than you're run-of-the-mill migraine. Most patients have a migraine phenotype to those post-traumatic headache. And so, I also did a similar study to that first migraine study. But it was very hard to actually recruit enough patients, in part because that study was done earlier on where there are a lot of restrictions on who can take part in the study. And due to other medications that patients may have been on or some other factors, it was just really tough to actually recruit enough patients. And so, at some point, I might discuss the findings from just those very few patients who took part. But it's hard to interpret because there are just so few patients who ended up taking part and also

completing the study. But again, with psychedelic studies now, the requirements for patients to take part have loosened up over the years. And so that's something I could revisit down the road.

Lindsay Weitzel, PhD:

I wanted to bring up something that I'm not sure if this was a misunderstanding or not. I know that early on, a lot of us were told that due to the type of receptor that psilocybin worked on, that if we had had a history of trouble with taking triptans, we should not be involved in psilocybin trials or look into using psilocybin if you were a cluster patient, etc. Is that true? Was that a misunderstanding when we didn't fully understand some of the receptors involved in psilocybin?

Emmanuelle Schindler, MD, PhD:

Well, if you look at a chemical structure of psilocybin and the chemical structure of a triptan, you may not be able to tell them apart because they look very similar. And not only chemically, but yes, pharmacologically they hit some of the same receptors. And even though triptans are designed to hit certain serotonin 1 receptors and psilocybin is best known as a serotonin 2A agonist, they have some activity at various serotonin receptors. So, it's not just one receptor that is responsible for either the clinical effect or if you've had side effects.

And depending on what someone means by I didn't tolerate one of the triptans, that might suggest that maybe psychedelics or psilocybin are not for you. For instance, we avoid triptans and patients who have had a heart attack or stroke because triptans, they can constrict blood vessels. And so if you really need to make sure that your blood vessels don't narrow down too much, then psychedelics might be risky for you as well, because they do the same thing.

And if someone has a really sensitive stomach, for instance, with the triptans, it can be really irritating to the stomach, well, most of your serotonin 2A receptors are in your gut or your blood vessels, not your brain. And so that's where GI side effects and also cardiovascular and cerebrovascular side effects, they can happen. So, there are some patients who probably should not try psychedelics, especially if they already have a contradiction to a triptan.

Lindsay Weitzel, PhD:

Interesting. I'm glad I brought that up. That was actually quite interesting. Something I wanted to ask is, if you can comment on how practical do you think this topic is to someone at this time who's sitting here listening because they have chronic cluster, chronic migraine, and nothing's helping them? Is there somewhere they can go to maybe get involved in a trial? What is your advice to that person that's really a listening hard?

Emmanuelle Schindler, MD, PhD:

Well, when it comes to headache disorders, we always need new treatments. And so, this is one of those potential new treatments that still needs to go through a lot of levels of research before it would be FDA approved. And then there's this other level of, well, it's out there and people are using it. It's important to also recognize that it's not just one drug company that is holding the medicine until it's ready to come out. So that's important for patients who, like you mentioned, might have tried numerous medications and are looking for something. But being aware that there are also risks to that,

number one, the drugs are still technically illegal. So then there are certain medical conditions where you would not want to take a psychedelic. But you can look on clinicaltrials.gov to see if there are trials that you can take part in. And then through that, there's a screening to screen out medical conditions where it's not safe to take psychedelic.

And then for practitioners too who are seeing headache patients, they might start or they have started hearing from their patients asking about psychedelics and headaches. It's important for them to know too, even though this is not something that you can prescribe yet. It's something that patients already have access to and might be curious about, might already be using. And so, a patient who's had a heart attack and has uncontrolled high blood pressure probably shouldn't be taking a psychedelic. It's important for headache providers to make sure to ask their patients, are you taking anything aside from what is being prescribed. And similarly, patients should feel safe telling their doctors and other practitioners what they're taking so that we know that it's safe.

Lindsay Weitzel, PhD:

Well, thank you for answering that. I think that's very important in case anyone's out there just wondering. Is there anything else you'd like to add to this awesome and unique topic before we go today?

Emmanuelle Schindler, MD, PhD:

I think I'll also add that I mentioned the looking at psilocybin and other psychedelics as a transitional treatment, so this short-term treatment with a long-lasting benefit. There's also evidence that it may have an acute effect, so to stop an individual migraine or an individual cluster attack. So, there is research going on with that too. And that's something that I recently talked about at the AAN meeting back in April. Cluster headache patients using DMT (dimethyltryptamine), which also looks very much like a triptan, to stop individual cluster attacks. And so that's not necessarily brand new because it's been going on for a few years. But that's a newer topic. But it's important to consider it very much depends on the pharmacology of the drug and how quickly it is metabolized, how fast it can work, and whether that could actually serve as an abortive treatment.

A slow onset, slow acting, psychedelic like LSD might not be the one that you want to take to stop an individual cluster attack. That's way too slow. And so, it's not that any psychedelic can substitute for another, and you can use it as an abortive or a transitional. It's important to consider how quickly it's acting, whether maybe this works well for a cluster, but not for migraine. No two headache disorders are the same. So that's also why earlier on I wanted to talk more about psychedelics and headache disorders because they're not all the same. There are many different flavors of each. And they're not all interchangeable. And so that's why we gather information from patients who might be trying it on their own. And then we're trying to do studies to try to break that down, which drugs are working for which condition and for which purpose. So, there's a lot of work ahead.

Lindsay Weitzel, PhD:

Oh, wow. Well, that was interesting. Thank you so much. I think when I first started talking to you, you were using ibuprofen as an analogy. There's many types of anti-inflammatories and there's many types of headache. And you're using that as an analogy. And I found that quite interesting. So, thank you so much for addressing that at the end here. Is there anything else you'd like to add before we go?

Emmanuelle Schindler, MD, PhD:

I think I'm good.

Lindsay Weitzel, PhD:

Well, thank you so much for being here today, Dr. Schindler. And thank you everyone for joining us. And please join us for the next episode of HeadWise. Bye bye

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